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THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of:
U.S. Patent No. 5,750,338

Mark L. Collins *et al.*

Reissue Serial No. 09/533,906

Reissue Application Filed: March 8, 2000

For: TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS

Group Art Unit: 1655

Examiner: D. Johannsen

TRANSMITTAL LETTER

ATTENTION: REISSUE LITIGATION BOX 7
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed are the following documents related to Reissue Application No. 09/533,906:

PROTEST UNDER 37 C.F.R. §1.291 – 20 pgs.

INFORMATION DISCLOSURE STATEMENT – 6 pgs.;

FORM PTO/SB/08 – 2 pgs. (in duplicate);

ELEVEN (11) REFERENCES;

PROOF OF SERVICE to Jean Burke Fordis, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P, Suite 700, 1300 I Street, N.W., Washington, D.C. 20005-3315 – 2 pgs; and

Certificate of Delivery

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is being hand delivered to the U.S. Patent and Trademark Office on the date indicated below addressed to the Commissioner for Patents, Reissue Litigation Box 7, Commissioner for Patents, Washington, D.C. 20231.

2/15/02
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sd-78998

No fee is believed due in connection with filing the Protest and related papers. If Protestor is incorrect and a fee is due, authorization is hereby provided to debit the appropriate fee from Account No. 03-1952, referencing Docket No. 474642800500.

Respectfully yours,

February 15, 2002

for Kate H. Murashige, Reg. No. 29,959 #43,48

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REISSUE LITIGATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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U.S. Patent No. 5,750,338

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For: TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS

Group Art Unit: 1655

Examiner: Johannsen, D.B.

PROTEST UNDER 37 C.F.R. § 1.291

ATTENTION: REISSUE LITIGATION BOX 7
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with 37 C.F.R. § 1.291, the following protest is submitted for consideration with regard to the examination of the above-referenced reissue application. Protestor is aware that this reissue application is involved in pending litigation based on the file history of the reissue application. This protest has been served on the reissue applicants in accordance with 37 C.F.R. § 1.248, as indicated by the attached proof of service.

REMARKS

The following remarks present arguments supporting the conclusion that U.S. Patent No. 5,750,338 should not be reissued because:

1. All claims are invalid as obvious under 35 U.S.C. § 103 based on prior art teachings cited herein;

2. Many claims are invalid as anticipated under 35 U.S.C. § 102 based on art cited herein;

3. The reissue oath/declaration filed with the application is defective under 37 C.F.R. 1.175 (and MPEP § 1414) for failure to identify a specific error which is relied upon to support the reissue application; and

4. The reissue oath/declaration filed with the application is defective under 35 U.S.C. § 101, 37 C.F.R. § 1.63 and MPEP 605.07 for failure to accurately identify all the joint inventors of the claimed invention.

1. ALL CLAIMS OF THE REISSUE APPLICATION ARE OBVIOUS BASED ON TEACHINGS IN THE PRIOR ART BEFORE DECEMBER 21, 1987.

The reissue application contains 59 pending claims: claims 1 to 40 are substantially the issued claims of the '338 patent, with one amendment to claim 19 presented in the Preliminary Amendment dated March 8, 2000; claims 41 to 59 were presented for examination in the Preliminary Amendment dated March 8, 2000. All pending claims are directed to methods (or a kit for carrying out such methods) for amplifying and/or detecting a target polynucleotide contained in a sample. Independent claims 1, 24, 27, and 34 are directed to methods of amplifying a target polynucleotide, and independent claims 7, 19, 28, and 38 are directed to methods of detecting a target polynucleotide. The independent "kit" claims are claims 20 and 24, which are "means for" claims (35 U.S.C. § 112, para. 6).

All claims that include an "amplifying" step can only claim priority to December 21, 1987, the filing date of a continuation-in-part application (Ser. No. 136,920) which added the first disclosure for this application series related to amplification. The parent application (Ser. No. 922,155) did not contain any disclosure related to "amplification" steps. Reissue applicant

has acknowledged that the present application is not entitled to the priority of the '155 application in p.6 of the Preliminary Amendment filed with the reissue application, where applicant treats December, 1987 as the relevant prior art date. Therefore, for the purposes of this protest, teachings in the prior art are those that were known before December 21, 1987.

A patent may not be allowed if the invention, though not identically disclosed or described in a single reference, would have been obvious to a person skilled in the relevant art at the time the invention was made (35 U.S.C. § 103(a)). Factual predicates underlying a determination of *prima facie* obviousness include the scope and content of the prior art, the differences between the prior art and the claimed invention, and the level of ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *In re Rouffet*, 149 F.3d 1350, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998). An invention is obvious if: (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or carry out the claimed process; and (2) the prior art would also have revealed that in so making or carrying out, those of skill in the art would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). When combining prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1456 (Fed. Cir. 1998). To provide such motivation, the prior art does not have to explicitly teach *how* to perform a method or make a composition, but must merely suggest to one of ordinary skill in the art that the combination of art would provide the solution to a problem. Motivation to combine references can be found when there is a close relationship between the problem to be solved, the applicable art, and the proposed solutions addressed in the art (*In re Inland Steel Company*, 60 USPQ2d 1396, 1402 (Fed. Cir. 2001)). For

biotechnology inventions such as claimed in this application, the level of ordinary skill in the art is generally quite high, e.g., a person having a Ph.D. or equivalent education and experience. The scope of the cited art and comparisons of the teachings of the art to the claimed invention are discussed in detail below.

All of the pending independent method claims comprise three essential steps: contacting a sample with a solid support that binds a target polynucleotide; separating the support and bound target polynucleotide from the sample; and amplifying the target polynucleotide. As demonstrated by the references discussed below, each of these steps was known in the prior art and the prior art provided explicit motivation to combine these steps. Therefore, Protestor submits that the pending claims are obvious under 35 U.S.C. § 103.

(1) Publications disclosing purification of viral RNA and *in vitro* amplification of the purified viral RNA

The pending claims are unpatentable over the combination of Pollet et al. (1967) "Replication of Viral RNA, XV. Purification and properties of Qß minus strands" *Proc. Natl. Acad. Sci. USA* 58 (2): 766-773, and Feix et al. (1968) "Replication of Viral RNA, XVI. Enzymatic synthesis of infectious viral RNA with noninfectious Qß minus strands as template" *Proc. Natl. Acad. Sci. USA* 59 (1): 145-152.

Pollet et al. (1967) disclose a method of purifying bacteriophage Qß "minus" strands from Qß viral RNA (a double-stranded RNA (dsRNA) comprising "minus" and "plus" strands). The minus strands are the target polynucleotide that is purified. This method uses the steps of:

1. Preparing a sample containing single-stranded viral RNA (ssRNA) by denaturing viral dsRNA into its plus and minus strands,

2. Contacting the sample with an excess of plus-strand fragments to make a hybridization mixture in which the plus-strand fragments replace the natural plus strands to form a dsRNA (i.e., made up of minus strand and plus-strand fragments), and contacting the sample with a solid support (cellulose particles) that separates dsRNA from ssRNA,
3. Separating the dsRNA from hybridized ssRNA and other sample components by cellulose chromatography,
4. Eluting and denaturing the dsRNA to form a mixture of minus strands and shorter plus-strand fragments which were separated by centrifugation, and collecting the longer strands to substantially separate the minus strands from plus-strand fragments,
5. To remove any remaining plus-strand fragments, the collected portion is heated to allow the minus strands to hybridize to any residual plus-strand fragments (i.e., a limited amount of dsRNA), which are then separated from the target minus strands by repeating the cellulose chromatography to retain the dsRNA, and collect the purified minus strands (ssRNA). This method substantially separates the target polynucleotide, the minus strands, from other sample components including non-target polynucleotides (e.g., plus strand fragments) by using a solid support that binds the target polynucleotide present in the sample.

Feix et al. (1968) disclose *in vitro* RNA synthesis using purified Qß minus strands (made essentially by the above-described method of Pollet et al.) as the template polynucleotide and using Qß replicase as the polymerase with appropriate nucleotide triphosphates in a salt buffer. The *in vitro* reaction produced an increased amount of

RNA (three times the input RNA after four minutes, as detected by radioactive product). The amplified RNA was detected by incorporation of radioactivity and was detected as biologically functional infectious units by using an *in vivo* transfection assay.

These two references together disclose: (1) purification of a target polynucleotide, a Qß RNA minus strand, from other sample components by steps that bind the target polynucleotide to a solid support, cellulose, such binding being effected by virtue of hybridizing the target polynucleotide to complementary oligonucleotides, and then separating the desired polynucleotide from other sample components, and (2) *in vitro* amplification of the target polynucleotide by synthesizing at least three-fold more RNA from this template using a polymerase, and detecting the amplified RNA as radioactively labeled RNA or functional products (infectious units). One would be motivated to combine the disclosures of these references because Feix et al. cite the Pollet et al. reference to provide detailed information on the method of purifying the minus strand RNA used as a template in the *in vitro* amplification of the RNA. Moreover, one skilled in the art would have known to combine these references because they are part of a series (the XV and XVI publications) of papers published by authors in Dr. Weissmann's research group.

The methods claimed in the pending reissue application comprise the steps of (a) contacting a sample with a first support that binds the target polynucleotide, (b) separating the support and bound target polynucleotide from the sample, and (c) amplifying the target polynucleotide. The specification (col. 2, lines 9-19) broadly

defines "amplify" as creating an amplification product, including additional target molecules or target-like molecules which are capable of functioning in a target-like manner or which are subject to detection in place of the target molecule. For target polynucleotides, such amplified products can be made enzymatically with DNA or RNA polymerases or transcriptases.

All of the elements in the claimed methods were disclosed in these two references. Pollet et al. disclose contacting a sample containing the target polynucleotide (minus strands) with a first support that binds the target polynucleotide (cellulose), and separating the support and bound target polynucleotide from the sample (chromatographic separation of dsRNA from ssRNA). Feix et al. disclose amplifying the target polynucleotide, the minus strands, in their *in vitro* synthesis reaction that produces more RNA from the purified minus strands by using a polymerase (a transcriptase, namely, Qß replicase). The newly synthesized RNA were detected (as infectious units). The *in vitro* synthesis reaction of Feix et al. is contained within the definition of "amplify" in the specification because it produces additional target molecules (minus strands) or target-like molecules (plus strands) and molecules subject to detection (radioactively labeled RNA and infectious units). Moreover, this synthesis appears to be exponential, based on the results of Feix et al. (see page 148, Table 3, Net Synthesis column, and page 150 , Fig. 2).

Both papers were published before the December 21, 1987 priority date of the application that resulted in issuance of the '338 patent. Therefore, a *prima facie* case of obviousness has been established for the methods claimed in the pending reissue application based on these two references. Based on the foregoing comments, Protestor submits that the pending claims must be deemed unpatentable over Feix et al. in view of Pollet et al. under 35 U.S.C. § 103.

(2) Additional Motivation is Provided in the Art to Combine Separation of a Target Polynucleotide from a Sample with Amplification

Protestor submits that the pending claims are unpatentable as obvious over the disclosure of Chu et al., U.S. Patent No. 4,957,858 (priority to U.S. application no. 852,692, filed April 16, 1986). Protestor notes that the filing date of the priority application was incorrectly printed on the face of the '858 patent but corrected by a certificate of correction. Thus, U.S. Patent No. 4,957,858 is prior art to this reissue application under 35 U.S.C. § 102(e).

Chu *et al.* disclose methods for detecting nucleic acids that employ a reporter group (RNA) that is capable of being autocatalytically replicated *in vitro* by a polymerase, namely the bacteriophage Qβ replicase. Chu et al. disclose that the *in vitro* amplification method is typically carried out on a sample which is a processed specimen, derived from a raw specimen by various treatments to remove materials that would interfere with detection (column 7, lines 10-17). In particular, Chu et al. state that the amplification method of the assay can be carried out on nucleic acids isolated from a specimen and deposited onto solid supports, such as by using a variety of known methods (column 7, lines 24-38).

The "Background" section of the specification of the reissue application makes clear that methods that use a first support that binds to the target polynucleotide, such as by using nucleic acid hybridization were known in the art at the time the invention was made. For example, see column 3, lines 12-16, and column 4, lines 21-27 and 30-45, and references cited therein. The specification also makes clear that methods of nucleic acid amplification (to produce multiple RNA transcripts or DNA copies) were known in the art at the time the invention was made, as were commercially available products that one skilled in the art could use to practice such amplification methods. For example, see column 30, line 59 to column 31, line 4, column 31, lines 29-39, and column 32, lines 12-17, and references cited therein. The prosecution history of the '338 patent, cited prior art teaching nucleic acid amplification by using the polymerase chain reaction (PCR) which was known to one skilled in the art at the time the claimed invention was made (e.g., U.S. Patent 4,965,188, Mullis et al., filed June 1987). Therefore, all of the steps of the present claims were known in the art at the time the invention was made. The motivation to combine known steps of sample purification and nucleic acid amplification is explicitly provided by Chu et al. who state that a nucleic acid amplification method can be carried out on nucleic acids isolated from a specimen and deposited onto solid supports. Thus, Chu et al. teach separation of the target polynucleotide from a sample by using a method that deposits the polynucleotide on a solid support, and nucleic acid amplification. Specific methods or procedures to practice separation of the target polynucleotide from a sample were known in the art as provided in applicant's own disclosure and in Chu et al., as were specific methods or procedures for amplifying a target polynucleotide. Chu et al. alone provide sufficient teachings to establish that the claimed methods would have been obvious to one skilled in the art at the

time the invention was made. Furthermore, Chu et al. provide motivation to one skilled in the art to combine known methods for separation of a target polynucleotide from a sample by using a solid support, and known methods of nucleic acid amplification, such as those described in the specification itself. Therefore, Protestor submits that the present claims must be rejected as *prima facie* obvious based on the teachings provided by Chu et al., alone or in combination with known prior art already cited in prosecution of this reissue application.

(3) Publications disclosing Nucleic Acid Separation and Signal Amplification

Reissue applicant has stated that separation of a target polynucleotide from a sample or from "background" components in the sample combined with nucleic acid amplification would not have been obvious because the prior art taught that one amplification method, PCR, could be practiced without sample isolation. That is, during prosecution of the '338 patent, reissue applicant argued that those skilled in the art would not have been motivated to combine target capture with PCR because PCR was considered highly specific only for its target sequence "so that additional steps for isolating target prior to amplification were not required." (See Dr. David Persing's declaration, filed on July 14, 1997, at page 6). Reissue applicant concludes that a person skilled in the art would not have been motivated to combine target polynucleotide separation steps with amplification steps at the time the invention was made. Applicant's conclusion is *not* supported by related prior art that taught target nucleic acid isolation from other sample components prior to signal amplification for the purpose of detecting the target polynucleotide. Signal amplification is within the scope of Applicant's definition of "amplify" because it produces "a molecule subject to detection steps in place of the target molecule, which

molecules are created by virtue of the presence of the target molecule in the sample." (See column 2, lines 9-15.)

Dattagupta et al., U.S. Patent No. 4,724,202 disclose sandwich hybridization methods that include using a labeled oligonucleotide or polynucleotide probe to hybridize to a target polynucleotide where the detection probe can be labeled with an enzyme in which case hybrids are detected by their ability to convert the enzyme's substrate to an optically or chemically distinguished product (see column 1, lines 23-32). Conversion of the substrate into detectable product is known to produce signal amplification because of the continuing enzymatic activity of the label. This reference further discloses that the method advantageously contacts under hybridization conditions, a separation probe immobilized to a solid support with an unknown sample and the labeled detection probe to produce a detectable amplified signal (see column 2, line 57 to column 3, line 9). Dattagupta et al. explicitly state the advantage of using such detection probes, i.e., they "exhibit greater sensitivity than heretofore by virtue of the far greater number of labels per single stranded nucleic acid probe than is possible by directly labeling the probe molecules" (column 8, lines 35-39). Thus, Dattagupta et al. teach one skilled in the art to use a method that includes a solid support to separate the target polynucleotide from other sample components and then to amplify the detectable signal to provide an assay with greater sensitivity for detection of the target polynucleotide.

Dattagupta et al., U.S. Patent No. 4,737,454 disclose other nucleic acid detection methods in which labels, such as those developed in the field of immunoassays, particularly enzymatically active groups, are attached to oligonucleotide probes which are then used to hybridize to a sample nucleic acid immobilized on a solid support (see column 5, lines 11-22 and column 8,

lines 27-31). Thus, Dattagupta et al. teach immobilization of a target polynucleotide to separate it from other sample components and amplification of the signal for detection.

Schneider et al., U.S. Patent No. 4,882,269, teach an amplified hybridization assay in which a "target DNA is allowed to anneal to an immobilized sequence that does not interfere with the binding of a primary probe, and the immobilized target is contacted with the primary probe and a family of secondary probes" (see column 15, lines 62-68). Schneider et al. teach the advantage of such an assay because "an enormously amplified signal is generated by the hybridization event" (see Abstract). Thus, Schneider et al. teach immobilization of a target polynucleotide and amplification of a signal for detecting the presence of the target polynucleotide.

Stuart et al., U.S. Patent No. 4,732,847, teach methods in which antibodies are used to determine the presence of a specific nucleic sequence on a solid support (see Abstract), and teach that by using antibodies the number of labels associated with binding "can be greatly amplified" (see column 4, lines 52-55). Thus, Stuart et al. teach binding of a target polynucleotide (a DNA-RNA hybrid) to a solid support to separate it from sample components and amplifying the signal for detection of the target polynucleotide.

The close relationship between the problems to be solved by this prior art and the methods of the pending claims makes this art relevant to an obviousness determination. That is, reissue applicant claims, and the prior art teaches, methods of substantially separating a target polynucleotide from "background" components by using a first support and then producing an amplified quantity of "a molecule subject to detection steps in place of the target molecule" ('338 specification, col. 2, lines 9-19) to detect the presence of the target polynucleotide. Based

on the proposed solutions addressed in the art, i.e., isolating the target polynucleotide and then amplifying a molecule to allow detection of the presence of the target polynucleotide, this art is relevant to an obviousness determination of the pending claims. At the time the invention was made, molecular biologists skilled in the art of detecting small quantities of target polynucleotides would have known this art and would have been taught by this art that methods to amplify the signal to be detected would provide the advantage of greater sensitivity to the assay. Therefore, one skilled in the art would have been motivated to use a step to amplify "a molecule subject to detection steps in place of the target molecule" whether that molecule was a transcript, copy, or other molecule that would signal the presence of the target polynucleotide. Thus, based on any combination of the above-cited art (U.S. Patent Nos. 4,724,202, U.S. Patent No. 4,737,454, U.S. Patent No. 4,882,269, and U.S. Patent No. 4,732,847) with methods already known in the art, as cited by the applicant in the specification or during previous prosecution, a person of ordinary skill in the art at the time the invention was made would have been motivated to combine method steps as presently claimed. That is, it would have been obvious to a person skilled in the art to combine steps to substantially separate a target polynucleotide from other sample components ("background" and inhibitor components) by binding the target polynucleotide to a first support, with a step of amplifying the separated target polynucleotide to achieve the advantage of a more sensitive and specific assay free of "background" interference. Therefore, the pending claims are unpatentable over the prior art under 35 U.S.C. § 103.

2. PENDING CLAIMS ARE INVALID AS ANCIPATED BY THE PRIOR ART UNDER 35 U.S.C. § 102(b)

To be anticipated under 35 U.S.C. § 102(b), all of the elements of the claimed invention must be described in a printed publication more than one year before the priority date of the

application for a patent. The reissue application priority date is 1987. Protestor respectfully submits that all of the essential steps of the independent method claims are described by Feix et al. (1968) "Replication of Viral RNA, XVI. Enzymatic synthesis of infectious viral RNA with noninfectious Qß minus strands as template" *Proc. Natl. Acad. Sci. USA* 59 (1): 145-152.

As discussed above, Feix et al. disclose *in vitro* RNA synthesis using purified Qß minus strands. Feix et al. describe a method (see page 146, paragraph 3) of substantially separating the target polynucleotide, the minus strands, from a sample by using a known method that uses a first support (cellulose particles) to bind the target polynucleotide. Feix et al. disclose to one skilled in the art a procedure to substantially separate the target polynucleotide from other sample components (e.g., "residual plus strands" or "double-stranded RNA") that would otherwise be "background" polynucleotides for subsequent steps. Feix et al. state that "contamination was small." Feix et al. then disclose amplifying the target polynucleotide and detecting the amplified product. Feix et al. describe amplifying the target polynucleotide in an *in vitro* reaction that uses a polymerase, specifically by using bacteriophage Qß replicase to incorporate appropriate nucleotide triphosphates into additional RNA molecules (e.g., see page 147, section following "*Minus strands as template for Qß replicase*"). The *in vitro* reaction taught by Feix et al. is "amplification" as defined in the reissue application specification (column 2, lines 9-19) because it produced an increased amount of RNA that "was created by virtue of the presence of the target molecule." Feix et al. showed that "After four minutes, the amount of RNA synthesized ... was equivalent to three times the input." (See Page 147, paragraph 3.) The amplified product was detected by incorporation of a

radioactive label (see Table 2, page 147). The amplified product was also detected by showing the formation of "infectious units" (i.e., bacteriophage plaques) as described at pages 149-150 (section following "*Time required for the synthesis of a plus strand*"). Thus, as defined in the specification at column 2, lines 13-14, Feix et al. produced RNA infectious units that are "molecule[s] subject to detection steps in place of the target molecule."

Thus, Feix et al. described all of the essential steps of the methods claims in the pending independent claims: separation of a target polynucleotide from sample using a first support, amplification of the target polynucleotide, and detection. Therefore, Protestor respectfully submits that the claims of the reissue application must be found anticipated by Feix et al.'s disclosure under 35 U.S.C. § 102(b).

3. THE REISSUE OATH/DECLARATION IS DEFECTIVE UNDER 37 C.F.R. 1.175.

An oath/declaration submitted with a request for reissue of a patent must identify a specific error which is relied upon to support the reissue application, under 37 C.F.R. 1.175 (see also MPEP § 1414). Reissue applicant has failed to state any error in the issued patent that makes the patent "wholly or partially invalid by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than the patentee had the right to claim in the patent" (37 C.F.R. 1.175 (a)(1)). Reissue applicant has failed to provide reference to a specific claim and specific claim language wherein the error lies which forms the basis for requesting reissue. Applicant has not narrowed nor broadened the independent claims submitted with this reissue application which might indicate that Applicant discovered an error that made the patent wholly or partially invalid. Applicant has merely added dependent claims that Applicant states is an

error because "the patent fails to contain claims of intermediate scope." It is respectfully sumibtted that failure to present dependent claims during prosecution that applicant subsequently might want to have issued is not an "error" as required by 37 C.F.R. 1.175(a). Applicant had the right to present dependent claims for examination during prosecution of the '338 patent and failed to present them, but that "error" does not make the issued '338 patent "wholly or partially invalid" because the scope of the issued claims is unchanged.

Furthermore, Hewlett-Packard Co. v. Bausch & Lomb, Inc., 882 F.2d 1556,1564-65, 11 U.S.P.Q.2d 1750, 1757 (Fed. Cir. 1989), cited in Assignee's Reissue Declaration dated March 8, 2000, supports Protestor's contention. In this case, the Court stated that "... a reissue applicant does not make a *prima facie* case of error in conduct merely by submitting a sworn statement which parrots the statutory language." Likewise, Applicant's Reissue Declaration has merely submitted "a sworn statement which parrots the statutory language" when it states that the '338 patent "is partially inoperative because, without any deceptive intention, the inventors claimed less than they had the right to claim in the patent."

Applicant's reissue application is therefore defective for failure to submit an oath/declaration in compliance with the requirements of 37 C.F.R. 1.175.

4. THE REISSUE OATH/DECLARATION IS DEFECTIVE UNDER 35 U.S.C. §101 AND 37 C.F.R. 1.172.

The Reissue Applicant for this application is the assignee as allowed under 37 C.F.R. 1.172 (a). Protestor however believes this oath is defective because all of the inventors of the claimed invention may not have assigned all of their rights to the invention to Applicant, i.e., the Applicant who signed the oath may not have the "entire interest" in the claimed invention.

Protestor believes that there is a question about the correct inventorship of the application, as required by 35 U.S.C. §§ 101 and 116, which names joint inventors. Therefore, a new declaration identifying and executed by each inventor in compliance with 37 C.F.R. 1.63(a) (see MPEP §§ 201.03 and 605.07) may be required.

Protestor notes that the inventors named in the reissue application are: Mark L. Collins, Donald N. Halbert, Walter King and Jonathan M. Lawrie. Protestor submits three publications that show that another person, Scott Decker, has been acknowledged by one of the named inventors in a manner that suggests that Scott Decker contributed to reduction to practice of the claimed invention.

D.V. Morrissey & M.L. Collins (1989) "Nucleic acid hybridization assays employing dA-tailed capture probes. Single capture methods." ***Molec. Cell. Probes*** **3: 189-207** describes hybridization techniques in which a "capture probe is immobilized on poly-styrene and used to capture target nucleic acids from the solution" which is used to "remove excess labeled probe and sample impurities" prior to detection (see Abstract). This publication by one of the inventors named in this reissue application describes isolation of a target polynucleotide in detail using a support to which the target polynucleotide binds. The "CONCLUSIONS" state that "The formats presented here can also be used to conveniently purify target from specimens prior to cloning or target amplification." Along with other steps described in the conclusion, "This would provide ... specificity to reduce backgrounds." "Further improvements in the sensitivity of the assay can be achieved not only with target amplification (data not shown)...." (See paragraphs 2 and 3 of the "CONCLUSIONS" section on page 205.) In the "ACKNOWLEDGEMENTS" section on the same page the authors state "We gratefully

acknowledge the contributions of our colleagues in this work: ... **Scott Decker for adapting the PCR to our method of doing target capture....**" (emphasis added). This acknowledgement by one of the named inventors of the reissue application, Mark L. Collins, acknowledges that Scott Decker probably reduced to practice the claimed invention of combining target polynucleotide capture as described in the paper with a nucleic amplification method, PCR. This suggests that Scott Decker contributed as an inventor to the method claims of this reissue application. Reissue applicants assert that their claims encompass specific and non-specific amplification methods although the specification teaches only non-specific amplification methods.

W.R. Hunsaker, H. Badri, M. Lombardo and M.L. Collins (1989) "Nucleic Acid Hybridization Assays Employing dA-Tailed Capture Probes. II. Advanced Multiple Capture Methods" ***Analytical Biochem.*** **181: 360-370** is another publication by one of the inventors, Mark L. Collins, named in the reissue application. This publication describes "reversible target capture" (RTC) in which a target nucleic acid released from a cell is captured by hybridization on oligo(dT) magnetic particles and then further purified from sample impurities by recapture (see Abstract). This publication describes "the background-reducing power of RTC" (see Abstract). The article describes methods of RTC in detail, using a variety of supports (e.g., oligo(dC) cellulose and poly(dT) nitrocellulose (see page 368, column 1). In the "DISCUSSION" the authors describe the limitations of assays based solely on PCR amplification or RTC and then state that "A technique combining signal or target amplification with reversible target capture should provide the greatest possible signal with a minimum of assay noise. Target capture can be used to rapidly purify the target from sample impurities and extraneous nucleic acids. The target can then be specifically amplified ...." (see page 369,

column 2). In the "ACKNOWLEDGMENTS" section on page 370, the authors state: "**We also thank Scott Decker for showing how RTC and PCR can be successfully combined.**" (emphasis added) This statement by Mark L. Collins, one of the inventors named in the reissue application, suggests again that Scott Decker contributed to reduction to practice of the claimed methods, i.e., the successful combination of target polynucleotide capture with nucleic acid amplification using the PCR method.

J.D. Thompson, S. Decker, D. Haines, R.S. Collins, M. Field and D. Gillespie (1989) "Enzymatic Amplification of RNA Purified from Crude Cell Lysate by Reversible Target Capture" *Clin. Chem.* 35/9: 1878-1881 describes procedures in which hybrids containing target polynucleotide are purified using "reversible target capture" followed by enzymatic amplification by the polymerase chain reaction method. This paper, authored by Scott Decker and others, shows the reduction to practice of the combination of RTC and PCR that the previous two cited papers acknowledged. Thus, one can conclude that these acknowledgements accurately state Scott Decker's contributions to the inventions claimed in this reissue application.

Because one of the inventors named in this reissue application repeatedly acknowledged in publications that Scott Decker contributed to reduction to practice of the target capture and amplification methods as claimed in the reissue application, the inventorship issue needs to be clarified and appropriate correction made, if needed. If inventorship is corrected, then the appropriate oath/declaration in compliance with 37 C.F.R. 1.63 will also be required.

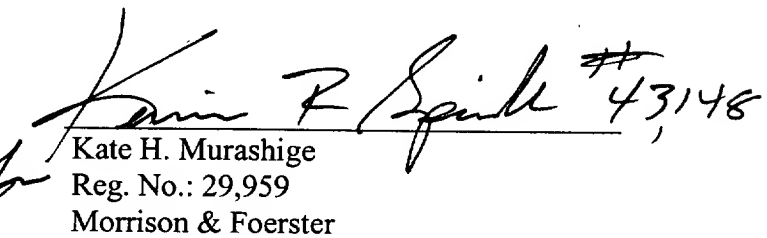
CONCLUSION

Protestor respectfully requests that the Examiner consider the above remarks when examining the reissue application of U.S. Patent No. 5,750,338. Based on the teaching of the art

cited herein and discussed above, Protestor has demonstrated that all of the pending claims of the reissue application are obvious under 35 U.S.C. § 103, or alternatively anticipated under 35 U.S.C. § 102. Further, Protestor respectfully submits that the Oath accompanying the reissue application was defective for two reasons: (1) it fails to comply with the requirement to identify a specific error which is relied upon to support the reissue application; and (2) not all of the joint inventors of the claimed invention may be named or have assigned the invention to Applicant.

Respectfully submitted,

Date: February 15, 2002



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